Patients Selected for Definitive Concurrent Chemoradiation at High-volume Facilities Achieve Improved Survival in Stage III Non–Small-Cell Lung Cancer

Elyn H. Wang, BS, Charles E. Rutter, MD, Christopher D. Corso, MD, PhD, Roy H. Decker, MD, PhD, Lynn D. Wilson, MD, MPH, Anthony W. Kim, MD, James B. Yu, MD, MHS, and Henry S. Park, MD, MPH

Background: The relationship between provider experience and clinical outcomes is poorly defined in radiation oncology. This study examined the impact of facility case volume on overall survival in patients with stage III non–small cell lung cancer (NSCLC) treated with definitive concurrent chemoradiation therapy (CCRT).

Methods: Using the National Cancer Data Base, we identified clinical stage III NSCLC patients diagnosed in 2004 to 2006 who were treated with definitive CCRT to 59.4–74.0 Gy. High-volume facilities (HVF) were defined as those in the ninetieth percentile of annual CCRT volume (≥12 cases/year). Independent predictors of receiving CCRT at HVF were identified using multivariable logistic regression. Overall survival based on receiving CCRT at HVF was assessed using Kaplan–Meier analysis, Cox proportional hazards regression, and propensity score matching.

Results: Among 10,072 included patients, 1207 (12.0%) were treated at HVF. Patients in HVF were more likely to have a higher Charlson–Deyo comorbidity score, more advanced nodal stage, higher doses, and 3D-conformal or intensity-modulated radiotherapy. When controlling for demographic and clinical covariates including academic affiliation, treatment at HVF was independently associated with a significantly decreased risk of death (hazards ratio = 0.93; 95% confidence interval: 0.87–0.99; $p = 0.03$). Propensity score matching showed that these findings were robust (hazards ratio = 0.91; 95% confidence interval: 0.84–0.99; $p = 0.04$).

Conclusions: Our findings suggest that treatment at HVF is associated with improved overall survival among stage III NSCLC patients receiving definitive CCRT, independent of academic affiliation. Further research is needed to determine whether or not efforts supporting centralization of radiotherapy at HVF will improve population-based survival, toxicities, and costs.

Key Words: Radiation therapy, facility volume, case volume, non–small-cell lung cancer, survival.

(*J Thorac Oncol.* 2015;10: 937–943)

Lung cancer remains the leading cause of cancer mortality in the United States, with approximately 224,000 new diagnoses and 159,000 deaths estimated in 2014.[1] Approximately 87% of these patients have nonsmall-cell lung cancer (NSCLC), and survival for locoregionally advanced disease is approximately 26% at 5 years after diagnosis.[2] For patients with locally advanced stage III NSCLC, National Comprehensive Cancer Network guidelines support the use of definitive concurrent chemoradiation therapy (CCRT) as a standard-of-care treatment option.[3] Numerous studies have identified greater provider experience and higher hospital volume as predictors of improved outcomes, particularly for patients undergoing specialized oncologic surgeries, such as pancreaticoduodenectomy or lung lobectomy.[4–18] However, few studies have investigated the association between case volume and patient outcomes for radiotherapy (RT), especially in lung cancer.[19–22]

RT treatment planning and delivery for NSCLC can be quite complex and variable given the myriad choices of radiation modalities, CCRT regimens, and protocols currently available.[23–26] In addition, high-volume facilities (HVF) have been reported to have higher rates of protocol compliance, a factor shown to correlate with improved outcomes.[27,28] CCRT for NSCLC is also frequently complicated by acute and chronic toxicities, often requiring a network of experienced diagnostic, therapeutic, and support services to ensure optimal patient outcomes.[29–31] Because of the increasingly complex and multidisciplinary nature of locally advanced NSCLC treatment, we hypothesize that treatment at HVF with expertise in treating a large number of CCRT cases may be associated with improved overall survival.

In the current study, we used data from the National Cancer Data Base (NCDB) for patients who were treated with

Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Dr. Yu and Dr. Decker receive research funding from twenty-first Century Oncology (ongoing). In addition, Dr. Yu receives research funding from the PhRMA Foundation (ongoing). Dr. Decker also receives research funding from Merck & Co., Inc. (ongoing) and has consulted for AMAG Pharmaceuticals, Inc. (past) and Leidos Biomedical Research, Inc. (ongoing). These funding sources had no involvement in the design, analysis, or preparation of the manuscript. The authors have no relevant conflicts of interest to disclose.

Address for correspondence: Henry S. Park, MD, MPH, Department of Therapeutic Radiology, Yale University School of Medicine, Smilow Cancer Hospital, 35 Park St, LL 509, New Haven, CT 06519. E-mail: henry.park@yale.edu

DOI: 10.1097/JTO.0000000000000519

ISSN: 1556-0864/15/1006-0937

definitive CCRT for stage III NSCLC diagnosed and clinically staged between 2004 and 2006. Our primary objective was to investigate the relationship between RT facility volume and overall survival. We also assessed potential associations between various demographic and clinicopathologic characteristics and receipt of RT at HVF versus low-volume facilities (LVF). Finally, we sought to identify other factors associated with improved survival among patients with locally advanced NSCLC who received CCRT.

MATERIALS AND METHODS

National Cancer Data Base

We performed a retrospective analysis of United States national practice using the NCDB. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It contains de-identified information from approximately 70% of newly diagnosed cancers in the United States. NCDB contains information that is unavailable in the surveillance, epidemiology, and end results database, including treatment details pertaining to RT dose, technique, and target. The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. The Yale Human Investigations Committee determined that this study was exempt from review given that it used existing and de-identified data.

Patient Identification

We identified patients 18 years of age or older treated with definitive CCRT with clinical stage III NSCLC (cT1-4/cN2-3/cM0, cT3-4/cN1/cM0, or cT4/cN0/cM0, based on American Joint Committee on Cancer 6th edition classification) who were diagnosed and clinically staged in 2004 to 2006. Included International Classification of Diseases-*O*-3 histology codes are listed in Supplemental Table 1 (Supplemental Digital Content, http://links.lww.com/JTO/A819). CCRT was defined as (1) starting RT within 30 days of chemotherapy initiation or (2) starting chemotherapy before the end of the RT course. We excluded patients with unknown vital status or follow-up information and those with missing information on facility type. In addition, patients who underwent surgical resection as part of the first planned course of treatment, who had unknown or missing treatment data, or did not receive RT at the reporting facility were excluded (Fig. 1). We further restricted our study population to patients who received a total RT dose within the range of 59.4 to 74.0 Gy in 30 to 37 fractions to reduce the potential for misclassification due to miscoding during data submission to NCDB.

Statistical Methods

To estimate RT facility volume, we assigned an average annual volume to each facility appearing in the NCDB. This was achieved by dividing the total number of CCRT cases reported by each facility by the number of years of accreditation between 2004 and 2006. Because the number of

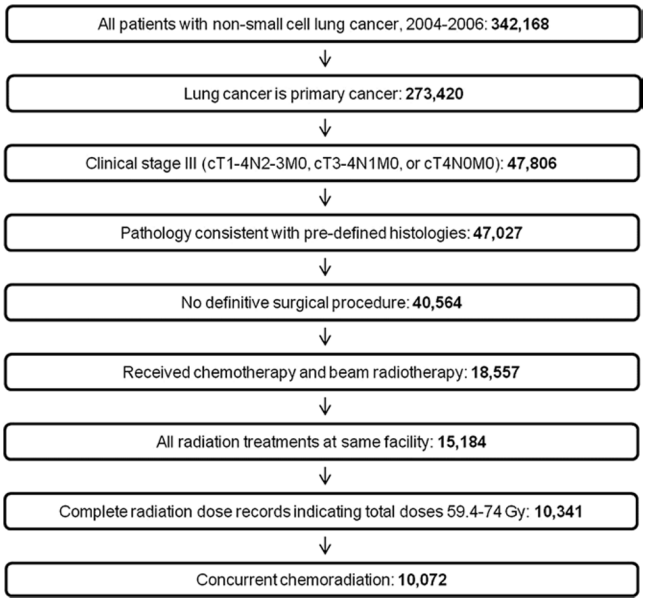

FIGURE 1. Exclusion criteria used to determine the final study cohort.

CoC-accredited cancer programs changes from one diagnosis year to the next, not all of the hospitals available in the NCDB were accredited for every one of the diagnosis years included over the study period. HVF were defined before analysis as those belonging in the ninetieth percentile of annual RT volume rounded to the nearest whole number, with the remainder aggregated as LVF.[32,33] We also performed a sensitivity analysis with alternative HVF definitions in an attempt to identify a threshold of facility case volume needed to achieve improved outcomes.

Demographic factors included in the analysis included age at diagnosis, race, 2000 census tract annual median income, insurance status, geographic region, patient location (rural, metro, and urban), travel distance to reporting facility, and Charlson/Deyo comorbidity score. Clinical characteristics, defined at the patient level, included RT modality (three-dimensional conformal RT, intensity-modulated RT, and nonconformal RT), total RT dose–fractionation, and year of diagnosis. Facility-level characteristics included hospital type and treatment volume. Classification of hospital academic status was made based on the cancer program category assigned by the CoC for each facility. Academic Comprehensive Cancer Program facilities (postgraduate medical education in at least four areas and more than 500 newly diagnosed cancer cases per year) were classified as academic, whereas Comprehensive Community Cancer Program (>500 newly diagnosed cancer cases per year), Community Cancer Program (100–500 newly diagnosed cancer cases per year), and other facilities were classified as nonacademic.

The NCDB requires hospital registries to update vital status and other information in 5-year cycles. At the time of the current study, overall survival was available for patients diagnosed up to 2006. Patients entered the study on their date of diagnosis and were followed until the most recent date of last contact, death, or the end of the study period. Our primary

outcome measure was overall survival because outcome data regarding locoregional control, distant control, and cancer-specific survival are not available in NCDB.

The distribution of categorical demographic, clinical, and facility details was compared between patients treated in HVF versus LVF using Pearson's χ^2 test and Wilcoxon-rank sum test, as appropriate. Multivariable logistic regression modeling was used to identify predictors of treatment at HVF versus LVF. Kaplan–Meier analysis was used to compare overall survival between patients receiving CCRT at HVF versus LVF. We used multivariable Cox regression modeling as the primary analytic strategy to determine the association between overall survival and facility volume after adjusting for all significant covariates.

Sensitivity analysis was performed using propensity-score matched pairs as an alternative method of comparison in the primary cohort. Propensity matching is a technique in which quasicase/control pairs are produced from a retrospective cohort to simulate randomized controlled trials that attempt to balance measured and unmeasured confounders.[34] For our cohorts, patients who received treatment in HVF were matched to patients treated at LVF who have a similar propensity of being treated in either facility type. Matching was performed after randomly ordering patients using the psmatch2 algorithm[35] in Stata SE version 13.0, with one to one nearest-neighbor matching without replacement.[36] Standard summary statistics were used to compare the baseline patient demographics, facility type, and clinicopathologic characteristics between groups of propensity-matched cases and controls. The matched cohorts (i.e., HVF vs. LVF) were compared using a log-rank test, and the hazards ratio (HR) was derived using univariable Cox regression.[37] A two-sided *p*-value of less than 0.05 was used to determine statistical significance. All analyses were performed using Stata SE version 13.0 (College Station, TX).

RESULTS

A total of 10,072 patients were included in our analysis. The range for facility volume was 1–28 CCRT cases each year with a median annual volume of 5.3 cases. The ninetieth percentile cutoff was identified as 12.3 (rounded to 12) cases per year. Therefore, 1207 (12.0%) patients were treated at HVF with ≥12 cases per year, and 8866 (88.0%) patients were treated at LVF with less than 12 cases per year.

Table 1 presents the demographic and clinical characteristics and treatment patterns of patients who were treated at HVF versus LVF. On multivariable logistic regression analysis, HVF were more likely to be categorized as an academic center than LVF (odds ratio = 4.28; 95% confidence interval [CI]: 3.72–4.93). Patients in HVF were also more likely to have a higher Charlson/Deyo comorbidity score, more advanced nodal stage, higher RT doses of 66.1–74.0 Gy compared with 59.4–66.0 Gy, and three-dimensional conformal RT or intensity-modulated RT compared with nonconformal RT (Table 2). Patients with non-Black race, who lived in counties with a higher median household income, or traveled a greater distance for treatment, were also more likely to undergo CCRT at HVF.

TABLE 1. Patient Demographic and Clinicopathologic Characteristics by Facility Volume Category

Characteristic	Low-Volume, N = 8865	High-Volume, N = 1207	*P* Value[a]
Facility type			<0.001
Nonacademic	6753 (92.0)	587 (8.0)	
Academic	2112 (77.3)	620 (22.7)	
Radiation dose			<0.001
59.4–66.0 Gy	7930 (88.9)	989 (11.1)	
66.1–74.0 Gy	935 (81.1)	218 (18.9)	
Radiation modality			<0.001
Intensity-modulated	202 (81.5)	46 (18.5)	
3D-conformal	1311 (85.8)	217 (14.2)	
Nonconformal	7352 (88.6)	944 (11.4)	
Facility location			<0.001
Northeast	1764 (89.5)	208 (10.5)	
South	2497 (80.1)	621 (19.9)	
Midwest	2904 (90.0)	322 (10.0)	
West	1700 (96.8)	56 (3.2)	
Sex			0.27
Male	5304 (88.3)	702 (11.7)	
Female	3561 (87.6)	505 (12.4)	
Age in years			0.67
18–59	2671 (88.4)	349 (11.6)	
60–69	3121 (87.5)	446 (12.5)	
70–79	2523 (88.1)	340 (11.9)	
≥80	550 (88.4)	72 (11.6)	
Race			0.39
White non-Hispanic	7328 (87.8)	1, 019 (12.2)	
Black	1150 (88.9)	144 (11.1)	
White Hispanic	138 (88.5)	18 (11.5)	
Other	239 (90.6)	26 (9.5)	
Primary payer			0.14
Private Insurance	302 (87.5)	43 (12.5)	
No insurance	3153 (88.9)	394 (11.1)	
Medicaid	563 (88.5)	73 (11.5)	
Medicare	4533 (87.6)	641 (12.4)	
Other government/ unknown	315 (84.9)	56 (15.1)	
Median income quartile			0.48
<$30,000	1428 (87.9)	196 (12.1)	
$30,000–35,000	1814 (89.1)	222 (10.9)	
$35,000–45,999	2626 (87.6)	373 (12.4)	
≥$46,000	2621 (87.9)	361 (12.1)	
Unknown	376 (87.0)	56 (13.0)	
Urbanization			0.002
Metro	6546 (88.7)	837 (11.3)	
Urban	1712 (86.7)	262 (13.3)	
Rural	607 (84.9)	108 (15.1)	
Year of diagnosis			0.11
2004	2940 (87.7)	414 (12.3)	
2005	2987 (87.4)	429 (12.6)	
2006	2938 (89.0)	364 (11.0)	

(*Continued*)

TABLE 1. (*Continued*)

Characteristic	Low-Volume, N = 8865	High-Volume, N = 1207	*P* Value[a]
T Stage			0.70
T1	1079 (87.2)	158 (12.8)	
T2	2933 (87.8)	408 (12.2)	
T3	1660 (88.3)	219 (11.7)	
T4	3193 (88.3)	422 (11.7)	
N Stage			0.02
N0	825 (90.6)	86 (9.4)	
N1	556 (90.1)	61 (9.9)	
N2	5627 (87.6)	796 (12.4)	
N3	1857 (87.6)	264 (12.4)	
Charlson–Deyo score			0.35
0	6321 (88.3)	839 (11.7)	
1	1953 (87.6)	277 (12.4)	
2	591 (86.7)	91 (13.3)	
Histology			0.21
Squamous cell	3281 (88.9)	411 (11.1)	
Large cell	372 (86.9)	56 (13.1)	
Adenocarcinoma	2226 (87.3)	325 (12.7)	
Other NSCLC	2987 (87.8)	415 (12.2)	
Travel distance			<0.001
<20 miles	6593 (89.8)	750 (10.2)	
≥20 miles	1990 (82.6)	418 (17.4)	
Unknown	282 (87.9)	39 (12.1)	

[a]The χ^2 test.

Median survival times were 19.7 months (95% CI: 18.3–20.9) for patients treated in HVF and 17.3 months (95% CI: 16.9–17.8) for patients treated in LVF ($p = 0.02$; Fig. 2*A*). After controlling for demographic and clinical factors in Cox proportional hazards modeling, treatment at HVF was independently associated with a decreased hazard of death (HR = 0.93; 95% CI: 0.87–0.99; $p = 0.03$; Table 3). Academic affiliation was not associated with overall survival (HR = 0.98; 95% CI: 0.93–1.03; $p = 0.42$).

Propensity score matching yielded 1207 pairs of patients who were treated at HVF and LVF. After propensity score matching, there were no meaningful differences on any observed measure between patients treated at HVF and LVF (Supplemental Table 2, Supplemental Digital Content, http://links.lww.com/JTO/A819). KaplanMeier survival analysis continued to show improved survival among patients in HVF ($p = 0.04$; Fig. 2*B*), and Cox proportional hazards modeling of the propensity score-matched cohort showed a similar survival benefit with treatment at HVF (HR = 0.91; 95% CI: 0.84–0.99; $p = 0.04$). Sensitivity analysis showed that when HVF was defined as facilities with at least 6, 7, 8, 9, 10, or 11 cases per year, volume was not associated with improved survival (Table 4).

DISCUSSION

We found that patients treated with definitive CCRT for stage III NSCLC in HVF (≥12 cases per year) achieved improved overall survival compared with LVF, independent

TABLE 2. Predictors of Treatment at High-Volume Facilities on Multivariable Logistic Regression Analysis

Characteristic (Reference)	Odds Ratio (95% Confidence Interval)	*P* Value
Facility type (nonacademic)		
Academic	4.28 (3.72–4.93)	<0.001
Radiation dose (59.4–66.0 Gy)		
66.1–74.0 Gy	1.52 (1.33–1.75)	<0.001
Radiation modality (nonconformal)		
3D-conformal	1.79 (1.25–2.57)	0.001
Intensity-modulated	1.43 (1.20–1.69)	<0.001
Facility location (Northeast)		
South	3.34 (2.76–4.05)	<0.001
Midwest	1.14 (0.94–1.39)	0.18
West	0.42 (0.31–0.58)	<0.001
Sex		
Female	1.10 (0.97–1.26)	0.15
Age in years (18–59)		
60–69	1.12 (0.94–1.34)	0.20
70–79	1.17 (0.94–1.46)	0.15
≥80	1.19 (0.87–1.63)	0.28
Race (White non-Hispanic)		
Black	0.75 (0.61–0.92)	0.007
White Hispanic	1.03 (0.58–1.80)	0.93
Other	0.90 (0.58–1.40)	0.63
Primary payer (private insurance)		
No insurance	0.95 (0.66–1.37)	0.78
Medicaid	0.92 (0.69–1.22)	0.56
Medicare	1.08 (0.90–1.29)	0.41
Other government/unknown	1.12 (0.80–1.57)	0.50
Median income quartile (<$30,000)		
$30,000–35,000	1.03 (0.82–1.28)	0.82
$35,000–45,999	1.42 (1.15–1.74)	0.001
≥$46,000	1.46 (1.17–1.83)	0.001
Unknown	1.45 (0.82–2.57)	0.21
Urbanization (metro)		
Urban	1.20 (0.99–1.45)	0.06
Rural	1.43 (1.05–1.93)	0.02
Year of diagnosis (2004)		
2005	0.98 (0.84–1.14)	0.77
2006	0.81 (0.69–0.95)	0.008
T stage (T1)		
T2	0.97 (0.79–1.20)	0.81
T3	0.96 (0.75–1.22)	0.75
T4	1.08 (0.86–1.34)	0.51
N stage (N0)		
N1	1.20 (0.82–1.75)	0.34
N2	1.40 (1.07–1.83)	0.01
N3	1.41 (1.05–1.89)	0.02
Charlson–Deyo score (0)		
1	1.17 (1.00–1.37)	0.047
2	1.37 (1.07–1.76)	0.01

(*Continued*)

TABLE 2. (*Continued*)

Characteristic (Reference)	Odds Ratio (95% Confidence Interval)	*P* Value
Histology (squamous cell)		
Large cell	1.33 (0.97–1.84)	0.08
Adenocarcinoma	1.18 (1.00–1.39)	0.06
Other NSCLC	1.08 (0.92–1.25)	0.35
Travel distance (<20 miles)		
≥20 miles	1.60 (1.36–1.88)	<0.001
Unknown	0.67 (0.35–1.40)	0.31

of academic affiliation. This effect was persistent after adjusting for covariates using multivariable Cox regression and on sensitivity analyses using propensity score matching. To our knowledge, this is the first study showing a provider volume–outcome relationship in definitive CCRT for NSCLC. Our findings are concordant with results from other studies showing that patients who receive cancer treatment at LVF have poorer survival. However, the majority of these studies focused on surgical volume, with the few

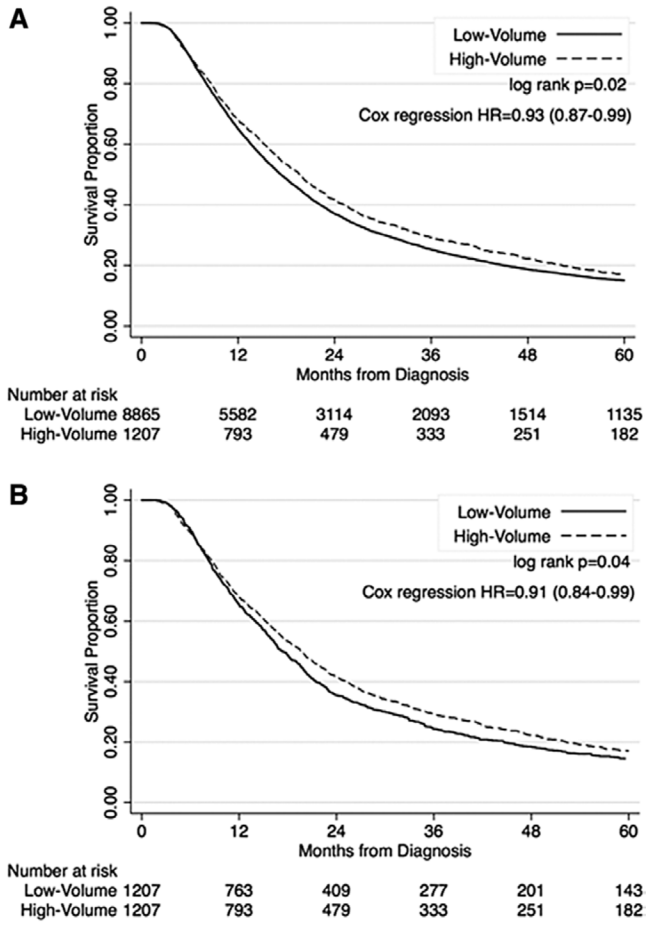

FIGURE 2. KaplanMeier estimates of overall survival according to facility volume category (*A*) before propensity score matching and (*B*) after propensity score matching.

TABLE 3. Cox Proportional Hazards Multivariable Model for Predictors of Overall Survival

Characteristic (Reference)	Hazard Ratio (95% Confidence Interval)	*P* Value
Facility volume (low-volume)		
High-volume	0.93 (0.87–0.99)	0.03
Facility type (nonacademic)		
Academic	0.98 (0.93–1.03)	0.42
Radiation dose (59.4–66.0 Gy)		
66.1–74.0 Gy	0.96 (0.92–1.01)	0.12
Radiation modality (nonconformal)		
3D-conformal	0.88 (0.76–1.01)	0.07
Intensity-modulated	0.94 (0.88–0.99)	0.03
Facility location (Northeast)		
South	1.03 (0.96–1.10)	0.40
Midwest	1.01 (0.95–1.07)	0.67
West	0.93 (0.87–1.01)	0.07
Sex		
Female	0.86 (0.82–0.90)	<0.001
Age in years (18–59)		
60–69	1.08 (1.01–1.14)	0.02
70–79	1.23 (1.15–1.33)	<0.001
≥80	1.44 (1.32–1.62)	<0.001
Race (White non-Hispanic)		
Black	0.90 (0.84–0.97)	0.002
White Hispanic	0.93 (0.78–1.11)	0.40
Other	0.86 (0.75–0.98)	0.03
Primary payer (private insurance)		
No insurance	1.10 (0.97–1.25)	0.13
Medicaid	1.09 (1.00–1.20)	0.07
Medicare	1.08 (1.02–1.15)	0.009
Other government/ unknown	1.10 (0.97–1.24)	0.12
Median income quartile (<$30,000)		
$30,000–35,000	0.93 (0.87–1.00)	0.06
$35,000–45,999	0.91 (0.85–0.98)	0.009
≥$46,000	0.87 (0.81–0.94)	<0.001
Unknown	0.86 (0.70–1.05)	0.15
Urbanization (metro)		
Urban	1.00 (0.94–1.06)	0.94
Rural	1.08 (0.96–1.20)	0.20
Year of diagnosis (2004)		
2005	0.94 (0.89–0.99)	0.01
2006	0.93 (0.88–0.98)	<0.001
T Stage (T1)		
T2	1.22 (1.13–1.31)	<0.001
T3	1.34 (1.24–1.46)	<0.001
T4	1.41 (1.31–1.52)	<0.001
N Stage (N0)		
N1	1.24 (1.11–1.39)	<0.001
N2	1.20 (1.11–1.31)	<0.001
N3	1.39 (1.27–1.52)	<0.001

(*Continued*)

TABLE 3. (*Continued*)

Characteristic (Reference)	Hazard Ratio (95% Confidence Interval)	*P* Value
Charlson–Deyo score (0)		
1	1.11 (1.06–1.17)	<0.001
2	1.22 (1.13–1.33)	<0.001
Histology (squamous cell)		
Large cell	0.92 (0.82–1.02)	0.12
Adenocarcinoma	0.96 (0.90–1.01)	0.12
Other NSCLC	1.00 (0.95–1.05)	0.85
Travel distance (<20 miles)		
≥20 miles	0.93 (0.88–0.99)	0.02
Unknown	1.00 (0.78–1.28)	1.00

assessments of RT volume examining practice for head and neck or cervical cancer.[13–22]

The underlying reasons for our finding of improved survival at HVF are unclear. The outcomes observed at HVF may be artificially influenced in either direction by referral patterns and selection bias. We found that patients from higher income regions, who had private insurance, and who traveled a greater distance to seek care were more likely to be treated at HVF. Thus, a possible explanation for the improved outcomes in these facilities may be that patients with greater access to economic and social resources may preferentially seek care at HVF.[7,17,38,39] Conversely, such patients could be more likely to be treated surgically after presenting to HVF, and so the remaining subset of patients treated at HVF who were found to be ineligible for surgery and therefore included in our analysis could be in a less favorable risk group than those at LVF. In addition, patients deemed to be at too high of a risk to undergo treatment at a LVF may be referred to HVF for more specialized treatment and supportive care. Despite these potential explanations, patients treated at HVF were found to be no healthier in terms of comorbidities or nodal status than those at LVF, and there was no evidence on propensity score matching that selection bias contributed strongly to our findings. We could not exclude the possibility that unmeasured variables like more guideline-supported contouring, higher rates of protocol compliance,[27,28] and the greater availability of experienced diagnostic, therapeutic, and supportive services[29–31] in both radiation oncology and medical oncology at HVF could explain our results. Improved multidisciplinary collaboration, more tumor site-specific specialists, and a differential ability to provide chemotherapy and radiation therapy at the same center may also be contributing to our results as well, though it is impossible to test for these hypotheses in the NCDB.

TABLE 4. Sensitivity Analysis Altering the High-Volume Facility Definition in the Cox Proportional Hazards Multivariable Model

High-Volume Facility Cut-off	Hazard Ratio (95% Confidence Interval)	*P* Value
6	0.99 (0.95–1.04)	0.82
7	1.00 (0.95–1.05)	0.95
8 (75th percentile)	0.97 (0.93–1.02)	0.29
9	0.96 (0.91–1.02)	0.19
10 (80th percentile)	0.95 (0.90–1.01)	0.09
11	0.95 (0.89–1.01)	0.09
12 (90th percentile)	0.93 (0.87–0.99)	0.03
Volume as continuous variable	1.00 (0.99–1.00)	0.09

Our findings that more advanced RT techniques were associated with improved survival are consistent with results from previous studies showing a benefit after adoption of computed tomography-based simulation for NSCLC.[40] It should be noted that facility volume was associated with improved survival even after controlling for radiation modality. We also found that doses of 59.4 to 66.0 Gy were associated with similar risk of death compared with doses of 66.1 to 74.0 Gy. These findings may appear to be discordant with RTOG 0617, which is a phase III study that revealed inferior survival for high-dose (74 Gy) compared to standard-dose RT[39]. However, they are consistent with recent data from a similar observational cohort showing no significant difference in survival among patients treated within a range of 59.4-74.0 Gy[40]. This may also reflect a role for an intermediate dose between 60 and 74 Gy.[43]

Our study has several other limitations to consider. First, there are several important clinical variables that we could not measure because NCDB lacked information regarding the patients' smoking status, performance status, and pulmonary function, which may also impact overall survival. We were also unable to examine survival among patients diagnosed after 2006. Although all patients in this study received CCRT, we could not identify the types of agents, number of agents, and number of cycles of chemotherapy used. It is also important to note that the NCDB facilities are likely to have treated more patients with thoracic RT than we have included in our study. Our analysis only reflects the number of definitive CCRT cases for NSCLC treated annually because we excluded patients receiving definitive or palliative RT alone, adjuvant or neoadjuvant RT with or without chemotherapy, sequential RT and chemotherapy, or any of the above for small-cell lung cancer. We intentionally restricted our sample in this way to minimize confounding by variations in disease risk or management approaches, but as a result, the generalizability of our findings may be limited. Finally, the magnitude of the survival benefit we observed by volume status is relatively small (increased median survival of 2.4 months), and so the clinical significance will need to be examined in greater depth by future studies.

In conclusion, we found that treatment at HVF performing ≥12 definitive CCRT cases per year for stage III NSCLC is associated with higher overall survival. Future studies should focus on identifying the factors responsible for this differential survival. Nevertheless, our study suggests that for stage III NSCLC patients receiving definitive CCRT, centralization of care to HVF may be a potential strategy to optimize patient outcomes.

REFERENCES

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
2. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014;64:252–271.
3. National Comprehensive Cancer Network: Non-Small Cell Lung Cancer (Version 1.2015). *J Natl Compr Canc Netw* 2014;12:1738–1761.
4. Meyerhardt JA, Catalano PJ, Schrag D, et al. Association of hospital procedure volume and outcomes in patients with colon cancer at high risk for recurrence. *Ann Intern Med* 2003;139:649–657.
5. Bach PB, Cramer LD, Schrag D, et al. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001;345:181–188.
6. Meyerhardt JA, Tepper JE, Niedzwiecki D, et al. Impact of hospital procedure volume on surgical operation and long-term outcomes in high-risk curatively resected rectal cancer: findings from the Intergroup 0114 Study. *J Clin Oncol* 2004;22:166–174.
7. Neighbors CJ, Rogers ML, Shenassa ED, et al. Ethnic/racial disparities in hospital procedure volume for lung resection for lung cancer. *Med Care* 2007;45:655–663.
8. Schrag D, Panageas KS, Riedel E, et al. Hospital and surgeon procedure volume as predictors of outcome following rectal cancer resection. *Ann Surg* 2002;236:583–592.
9. Schrag D, Panageas KS, Riedel E, et al. Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection. *J Surg Oncol* 2003;83:68–78; discussion 78.
10. Chen AY, Pavluck A, Halpern M, Ward E. Impact of treating facilities' volume on survival for early-stage laryngeal cancer. *Head Neck* 2009;31:1137–1143.
11. Park HS, Detterbeck FC, Boffa DJ, et al. Impact of hospital volume of thoracoscopic lobectomy on primary lung cancer outcomes. *Ann Thorac Surg* 2012;93:372–379.
12. Park HS, Roman SA, Sosa JA. Outcomes from 3144 adrenalectomies in the United States: which matters more, surgeon volume or specialty? *Arch Surg* 2009;144:1060–1067.
13. Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. *J Am Coll Surg* 2008;207:510–519.
14. Lüchtenborg M, Riaz SP, Coupland VH, et al. High procedure volume is strongly associated with improved survival after lung cancer surgery. *J Clin Oncol* 2013;31:3141–3146.
15. Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998;280:1747–1751.
16. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery* 1999;125:250–256.
17. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137.
18. Birkmeyer JD, Warshaw AL, Finlayson SR, et al. Relationship between hospital volume and late survival after pancreaticoduodenectomy. *Surgery* 1999;126:178–183.
19. Wuthrick E, Zhang Q, Machtay M, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. *J Clin Oncol.* 2015;33:156–164.
20. Chen AY, Fedewa S, Pavluck A, Ward EM. Improved survival is associated with treatment at high-volume teaching facilities for patients with advanced stage laryngeal cancer. *Cancer* 2010;116:4744–4752.
21. Lin JF, Berger JL, Krivak TC, et al. Impact of facility volume on therapy and survival for locally advanced cervical cancer. *Gynecol Oncol* 2014;132:416–422.
22. Lee MS, Tsai SJ, Lee CC, et al. Higher caseload improves cervical cancer survival in patients treated with brachytherapy. *Radiat Oncol* 2014;9:234.
23. Reboul FL. Radiotherapy and chemotherapy in locally advanced non-small cell lung cancer: preclinical and early clinical data. *Hematol Oncol Clin North Am* 2004;18:41–53.
24. Bayman N, Blackhall F, McCloskey P, et al. How can we optimise concurrent chemoradiotherapy for inoperable stage III non-small cell lung cancer? *Lung Cancer* 2014;83:117–125.
25. Biswas T, Sharma N, Machtay M. Controversies in the management of stage III non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2014;14:333–347.
26. Robinson LA, Wagner H Jr, Ruckdeschel JC. Treatment of stage IIIA non-small cell lung cancer. *Chest* 2003;123:202s–220s.
27. Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol* 2010;28:2996–3001.
28. Ohri N, Shen X, Dicker AP, et al. Radiotherapy protocol deviations and clinical outcomes: a meta-analysis of cooperative group clinical trials. *J Natl Cancer Inst* 2013;105:387–393.
29. Koning CC, Wouterse SJ, Daams JG, et al. Toxicity of concurrent radiochemotherapy for locally advanced non–small-cell lung cancer: a systematic review of the literature. *Clin Lung Cancer* 2013;14:481–487.
30. Chen C, Uyterlinde W, Sonke JJ, et al. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. *Radiother Oncol* 2013;108:337–341.
31. Dilling TJ, Extermann M, Kim J, et al. Phase 2 study of concurrent cetuximab plus definitive thoracic radiation therapy followed by consolidation docetaxel plus cetuximab in poor prognosis or elderly patients with locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014;90:828–833.
32. Tuggle CT, Patel A, Broer N, et al. Increased hospital volume is associated with improved outcomes following abdominal-based breast reconstruction. *J Plast Surg Hand Surg* 2014;48:382–388.
33. Gratian L, Pura J, Dinan M, et al. Treatment patterns and outcomes for patients with adrenocortical carcinoma associated with hospital case volume in the United States. *Ann Surg Oncol* 2014;21:3509–3514.
34. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:15.
35. Leuven E, Sianesi B: PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. Statistical Software Components S432001, Boston College Department of Economics. http://EconPapers.repec.org/RePEc:boc:bocode:s432001.
36. Gershengorn HB, Wunsch H, Scales DC, et al. Association between arterial catheter use and hospital mortality in intensive care units. *JAMA Intern Med* 2014;174:1746–1754.
37. Sher DJ, Koshy M, Liptay MJ, Fidler MJ. Influence of conformal radiotherapy technique on survival after chemoradiotherapy for patients with stage III non-small cell lung cancer in the National Cancer Data Base. *Cancer* 2014;120:2060–2068.
38. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–2127.
39. Lucas FL, Stukel TA, Morris AM, et al. Race and surgical mortality in the United States. *Ann Surg* 2006;243:281–286.
40. Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *J Clin Oncol* 2011;29:2305–2311.
41. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187–199.
42. Koshy M, Malik R, Sher DJ, et al. The effect of radiotherapy dose on survival in stage III non-small-cell lung cancer patients undergoing definitive chemoradiotherapy. *Clin Lung Cancer* 2014;15:365–371.
43. Rodrigues G, Senan S, Oberije C, et al. Is intermediate radiation dose escalation with concurrent chemotherapy for stage III non-small cell lung cancer beneficial? A multi-institutional propensity-score matched analysis. *Int J Radiat Oncol Biol Phys* 2014;90:S654–S654.

